THE UNIVERSITY OF CHICAGO MEDICINE

Potential Role of PARP Inhibition in the Management of Breast Cancer

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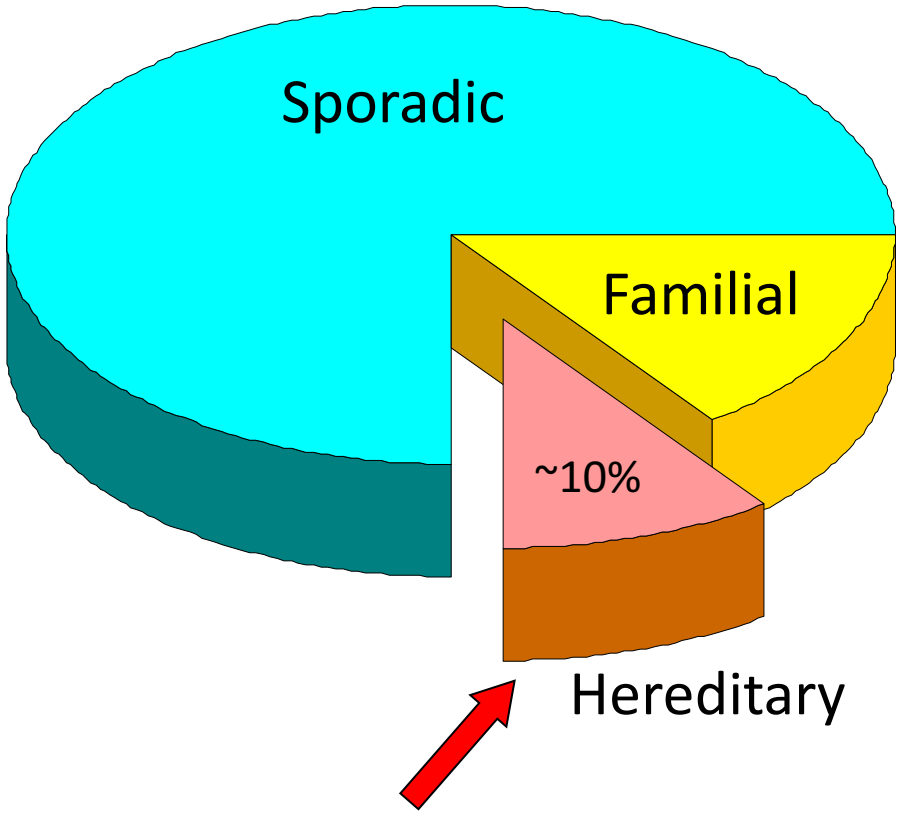
Disclosures

Advisory Committee	Celgene Corporation, Pfizer Inc
Contracted Research	Celgene Corporation, Genentech BioOncology, Merck

How much of breast cancer is hereditary?



- Sporadic cancer (70%)
  - By chance
- Familial cancer (15-20%)
  - Environment + genes
- **Hereditary cancer (10%)**
  - Inherited DNA mutation

When to suspect a hereditary syndrome

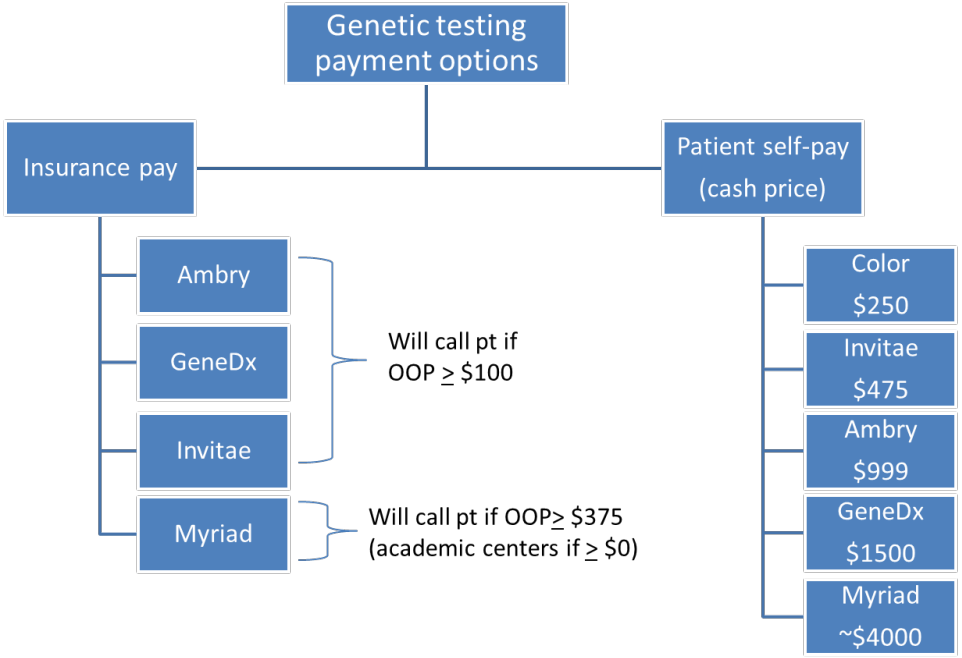
- Early onset breast cancer
- Bilateral breast cancer/multiple cancers
- Multiple family members/generations with cancer
- Clustering of certain cancers in family
- Rare cancers
- Populations with certain cancer gene mutations (e.g., Ashkenazi Jewish)
- Tumor mutation testing suggesting possible germline mutation

Indications for testing-NCCN guidelines

- Individual from a family with a known deleterious *BRCA1/BRCA2* gene mutation
- Personal history of breast cancer[b] + one or more of the following:
  - Diagnosed ≤45 y
  - Diagnosed ≤50 y with:
    - ◊ An additional breast cancer primary[c]
    - ◊ ≥1 close blood relative[d] with breast cancer at any age
    - ◊ ≥1 close relative with pancreatic cancer
    - ◊ ≥1 relative with prostate cancer (Gleason score ≥7)
    - ◊ An unknown or limited family history[a]
  - Diagnosed ≤60 y with:
    - ◊ Triple negative breast cancer
  - Diagnosed at any age with:
    - ◊ ≥2 close blood relatives with breast cancer, pancreatic cancer or prostate cancer (Gleason score ≥7) at any age
    - ◊ ≥1 close blood relative[d] with breast cancer diagnosed ≤50 y
    - ◊ ≥1 close blood relative[d] with ovarian[e] carcinoma
    - ◊ A close male blood relative[d] with breast cancer
    - ◊ For an individual of ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish) no additional family history may be required[f]
- Personal history of ovarian[e] carcinoma
- Personal history of male breast cancer
- Personal history of prostate cancer (Gleason score ≥7) at any age with ≥1 close blood relative[d] with ovarian carcinoma at any age or breast cancer ≤50 y or two relatives with breast, pancreatic, or prostate cancer (Gleason score ≥7) at any age
- Personal history of pancreatic cancer at any age with ≥1 close blood relative[d] with ovarian carcinoma at any age or breast cancer ≤50 y or two relatives with breast, pancreatic cancer, or prostate cancer (Gleason score ≥7) at any age
- Personal history of pancreatic cancer and Ashkenazi Jewish ancestry
- *BRCA1/2* mutation detected by tumor profiling in the absence of germline mutation analysis
- Family history only (significant limitations of interpreting test results for an unaffected individual should be discussed):
  - First- or second-degree blood[d] relative meeting any of the above criteria
  - Third-degree blood[d] relative who has breast cancer[b] and/or ovarian[e] carcinoma and who has ≥2 close blood relatives[d] with breast cancer (at least one with breast cancer ≤50 y) and/or ovarian[e] carcinoma

NCCN Guidelines Version 1.2017
BRCA-Related Breast and/or Ovarian Cancer Syndrome

Testing Options and Cost



Panel Testing

- Pros
  - Can test for multiple genes in single test
  - Cost effective
  - Time saving
  - Improved detection rate in families with atypical presentations
- Cons
  - Incidental findings-don't fit family history
  - Mutations in genes of limited clinical utility
  - High rate of VUSs

Phase 2 studies of olaparib reported to date

	Study 8[1]	Study 20[2]	Study 42[3]
Patient population	Locally advanced/metastatic *BRCA*m BC, ≥1 chemotherapy regimen	Advanced metastatic or recurrent BC, triple negative or known *BRCA*m	Advanced *BRCA*m BC that progressed despite ≥3 previous lines of chemotherapy for advanced/metastatic disease
Prior lines of therapy for advanced disease	3 chemotherapy regimens (median)	3 chemotherapy regimens (median)	4.6 (mean)
ORR	41%	0% (50% unconfirmed in *BRCA*m)	13%
CBR	56%	38% (in *BRCA*m)	60%
Median DoR	144 days	-	204 days

	Olaparib 400mg twice daily (n=27)			
	BRCA1 **(n=18)**	***BRCA2*** **(n=9)**	**Triple Negative (n=13)**	**Non-triple Negative (n=14)**
Objective Response	9 (50%)	2 (22%)	7 (54%)	4 (29%)
Complete Response	1 (6%)	0	0	0
Partial Response	8 (44%)	2 (22%)	7 (54%)	4 (29%)

Early studies demonstrated evidence of activity of olaparib monotherapy in heavily pretreated gBRCA-associated MBC

1. Tutt A, et al. *Lancet.* 2010;376:235-244. 2. Gelmon KA et al. *Lancet Oncol*. 2011;12:852-861. 3. Kaufman B, et al. *J Clin Oncol.* 2015;33:244-250.

OlympiAD study design

- HER2-negative metastatic BC
  - ER+ and/or PR+ or TNBC
- Deleterious or suspected deleterious g*BRCA*m
- Prior anthracycline and taxane
- ≤2 prior chemotherapy lines in metastatic setting
- HR+ disease progressed on ≥1 endocrine therapy, or not suitable
- If prior platinum use
  - No evidence of progression during treatment in the advanced setting
  - ≥12 months since (neo)adjuvant treatment

Olaparib
300 mg tablets bd

2:1 randomization

Chemotherapy treatment of physician's choice (TPC)
- Capecitabine
- Eribulin
- Vinorelbine

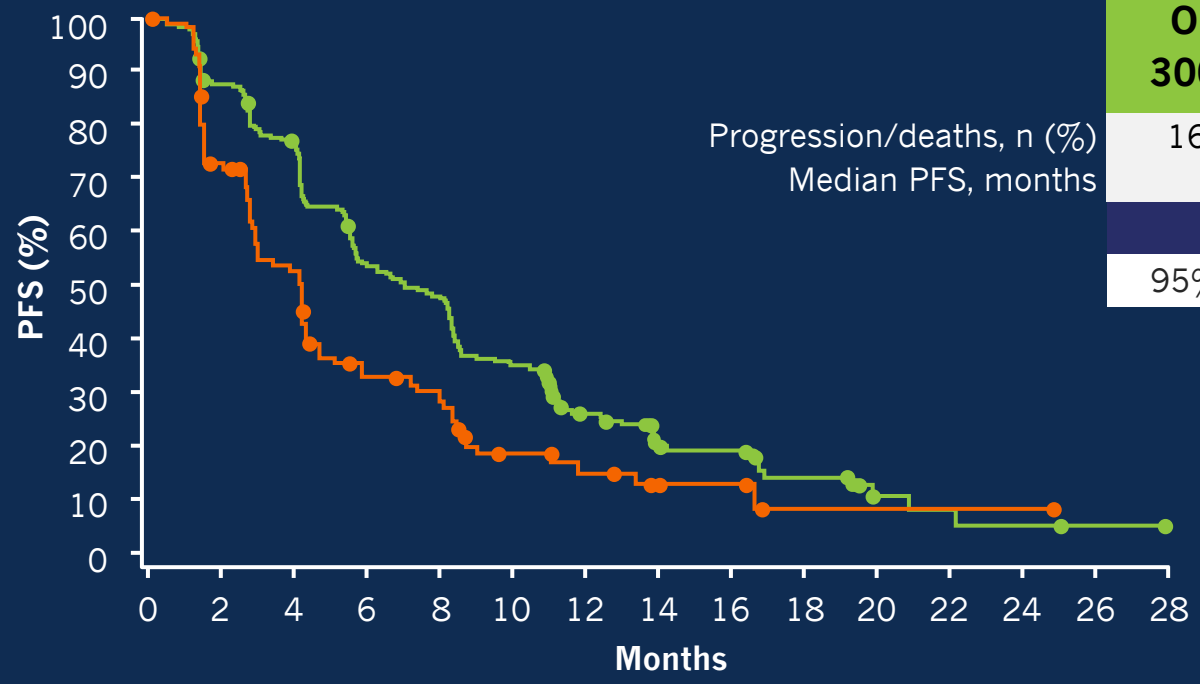
Treat until progression

Primary endpoint:
- Progression-free survival (RECIST 1.1, BICR)

Secondary endpoints:
- Time to second progression or death
- Overall survival
- Objective response rate
- Safety and tolerability
- Global HRQoL (EORTC-QLQ-C30)

BICR, blinded independent central review; ER, estrogen receptor; HR, hormone receptor; HRQoL, health-related quality of life; PR, progesterone receptor; RECIST, response evaluation criteria in solid tumors; TNBC, triple negative breast cancer

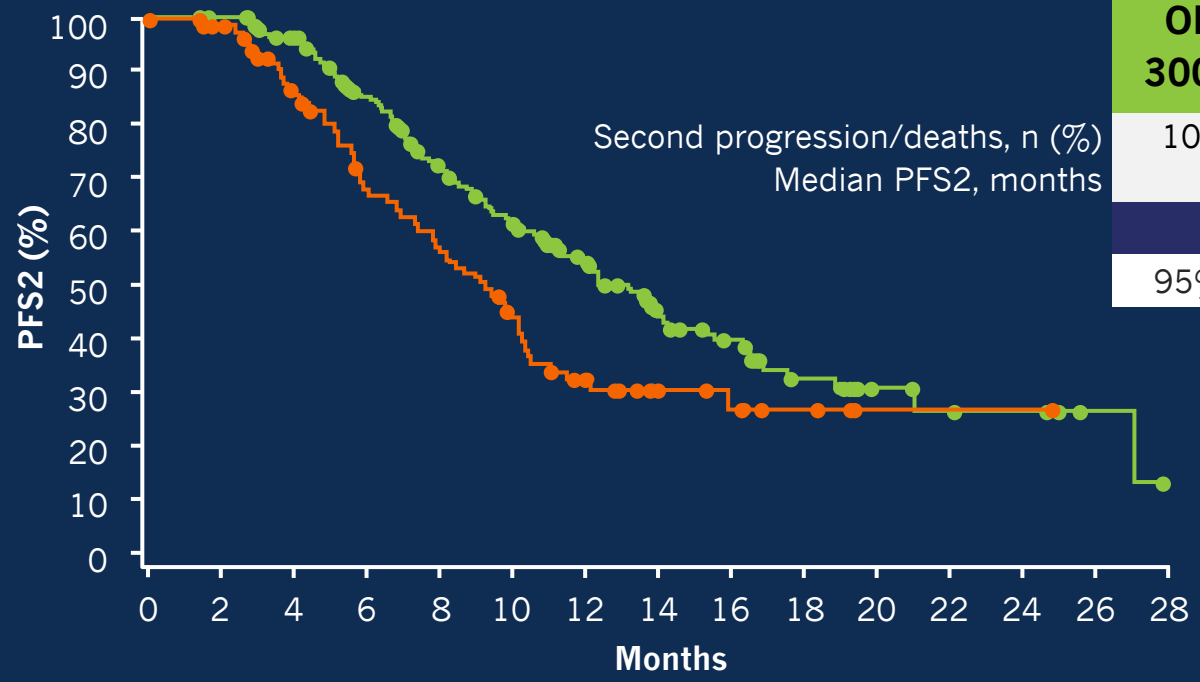
Primary endpoint: progression-free survival by BICR



	Olaparib 300 mg bd	Chemotherapy TPC
Progression/deaths, n (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2
HR 0.58		
95% CI 0.43 to 0.80; *P*=0.0009		

Presented by: Mark Robson, MD

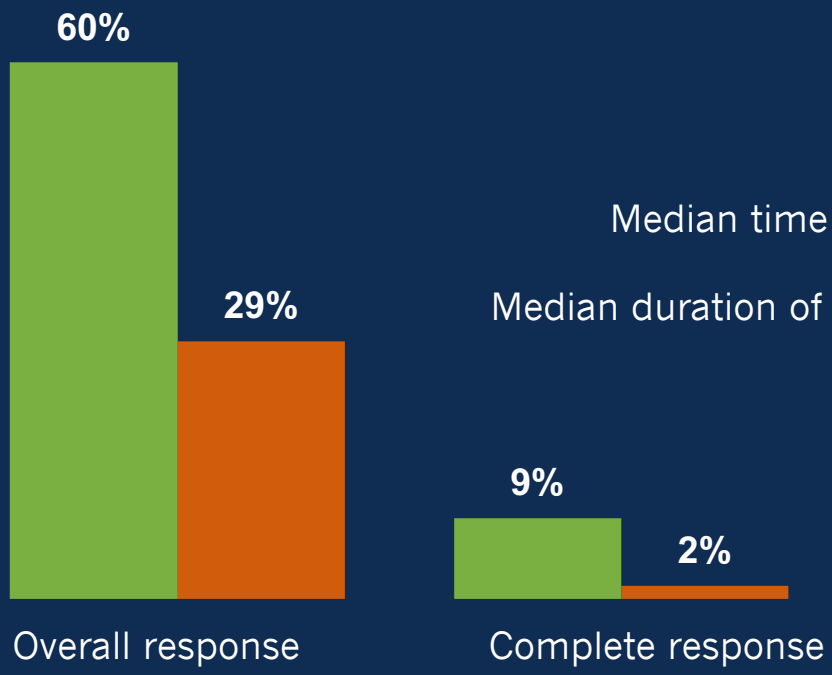
Time to second progression or death (PFS2) by investigator assessment



	Olaparib 300 mg bd	Chemotherapy TPC
Second progression/deaths, n (%)	104 (50.7)	53 (54.6)
Median PFS2, months	13.2	9.3
HR 0.57		
95% CI 0.40 to 0.83; *P*=0.0033		

Presented by: Mark Robson, MD

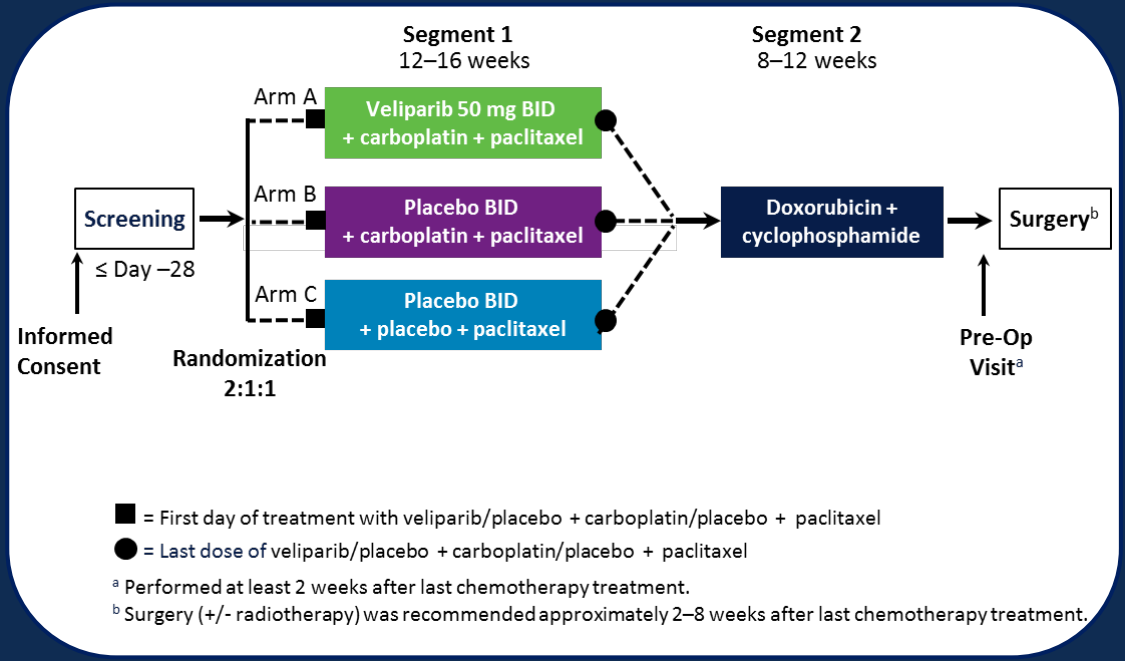
Objective response by BICR



	Olaparib 300 mg bd	Chemotherapy TPC
n	167	66
Median time to response, days	47	45
Median duration of response, months	6.2 (4.6–7.2)	7.1 (2.8–12.2)

Presented by: Mark Robson, MD

BRIGHTNESS Study Design



Study Objectives

Primary objectives:

- pCR

Secondary objectives:

- EFS, OS, breast conservation rate

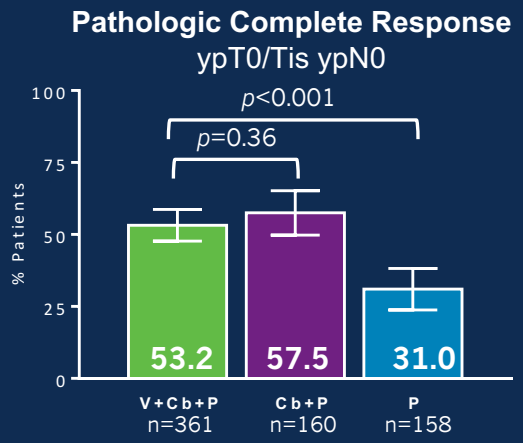
Tertiary objectives:

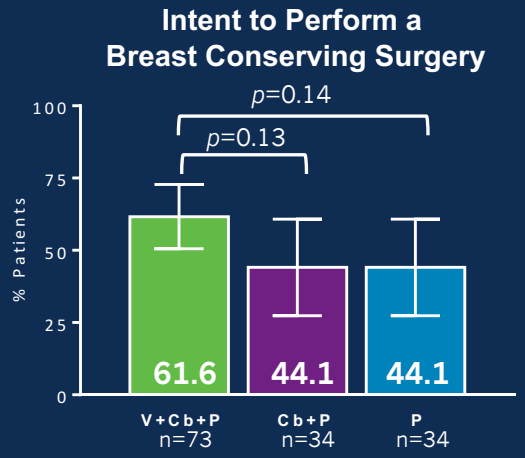
- MRI, near pCR, QoL

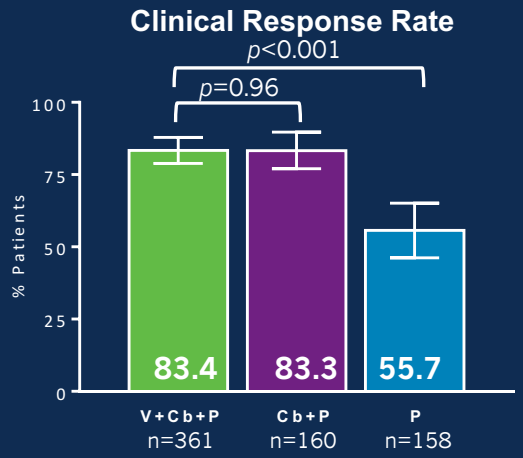
Presented by: Charles E. Geyer

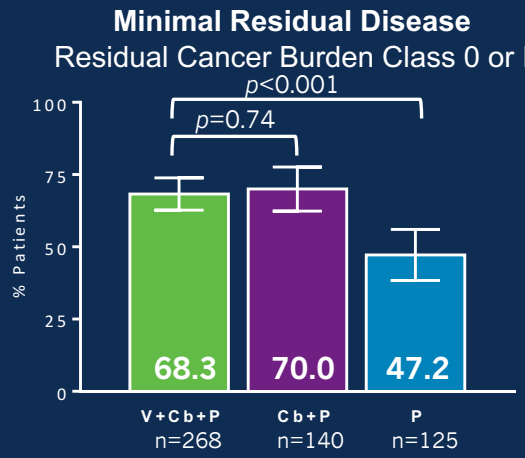
Efficacy

- Addition of veliparib and carbo significantly improved pCR over control (53.2% vs 31.0%, *p*<0.001) confirming results of I-SPY-2.
- Addition of veliparib to carbo/paclitaxel did not demonstrate improvement in pCR compared to carbo/paclitaxel arm (53.2% vs 57.5%, *p*=0.36).
- Increase in pCR with addition of carboplatin was independent of g*BRCA* mutation status.



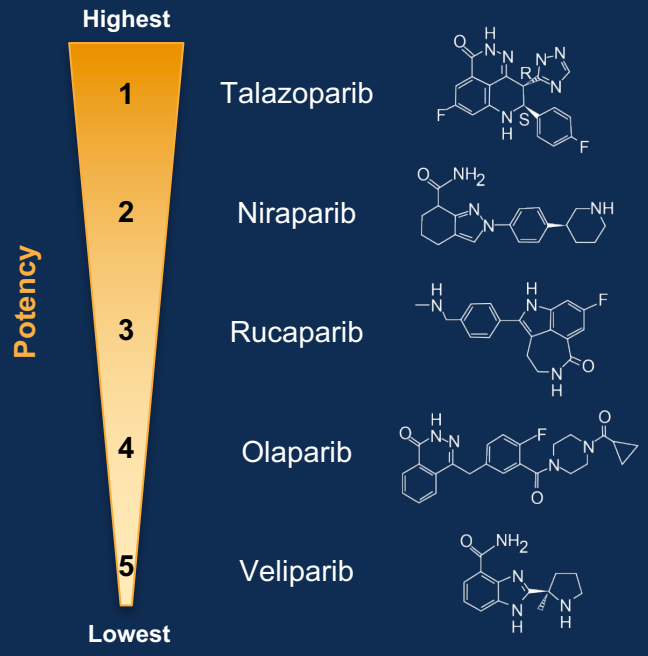




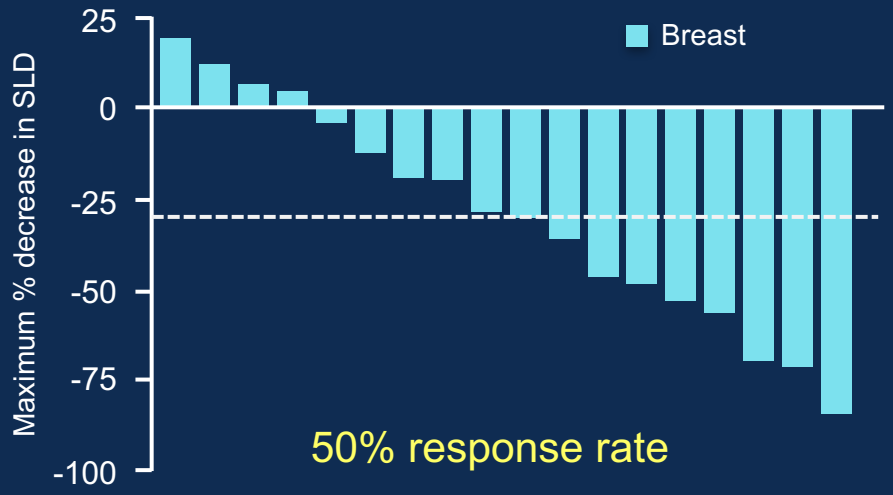


Background – Talazoparib

Talazoparib is a highly potent inhibitor of PARP[1]



Phase 1 trial – 18 breast cancer patients with *BRCA1/2* germline mutations[2]



Graph shows percentage change in target lesion for patients undergoing treatment with talazoparib who have g*BRCA* breast cancer. Positive values indicate tumor growth, negative values indicate tumor reduction, and the dashed line represents the definition of partial response from RECIST guidelines. Patients from parts 1 and 2 of the trial are included.
Abbreviation: SLD, sum of longest diameter.

1. Lord CJ, Ashworth A. *Science*. 2017;355:1152-1158; 2. de Bono J et al. *Cancer Discov*. 2017 Feb 27. doi: 10.1158/2159-8290.CD-16-1250.

ABRAZO Phase 2 Clinical Trial – Key Eligibility Criteria

- Patients with advanced breast cancer who carry a deleterious or suspected deleterious germline *BRCA1/2* mutation (by central laboratory or a local report approved by the sponsor)
  - **Cohort 1**: PR or CR to last platinum-containing regimen for metastatic disease with disease progression > 8 weeks following the last dose of platinum
  - **Cohort 2**: 3 or more prior cytotoxic regimens for metastatic disease; no prior platinum for metastatic disease
- Measurable disease by RECIST v1.1
- ECOG performance status 0 or 1
- Adequate organ and bone marrow function
- CNS metastases permitted, provided stable following local therapy
- HER2+ breast cancer permitted, provided the patient's disease is refractory to HER2-targeted therapy
- Washout from prior therapy (systemic therapy, RT, surgery): 14 days

Abbreviations: CNS, central nervous system; CR, complete response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors version 1.1; RT, radiation therapy.

Primary Efficacy Endpoint – ORR by Independent Radiologist Facility

	Cohort 1 Prior Platinum (n = 48)	Cohort 2 3L+, No Prior Platinum (n = 35)	Total (N = 83)
Objective response rate, % (95% CI)	21 (10-35)	37 (22-55)	28 (18-39)
Best overall response, % (No.)			
Complete response	4 (2)	0	2 (2)
Partial response	17 (8)	37 (13)	25 (21)
Stable disease	38 (18)	51 (18)	43 (36)
Progressive disease	38 (18)	11 (4)	27 (22)
Not evaluable	4 (2)	0	2 (2)

Similar RR in BRCA1 vs BRCA2 (23% vs 33%)
Similar RR in TNBC vs non-TNBC (26% vs 29%)

Presented by: Nicholas C. Turner

Select ongoing trials of PARPi in advanced breast cancer

Name	Phase	Arms	Eligibility	Clinicaltrials.gov
BROCADE	III	paclitaxel/carbo +/- veliparib	• gBRCA1/2	NCT02163694
BRAVO	III	niraparib vs TPC	• gBRCA1/2	NCT01905592
S1416	II	cisplatin +/-veliparib	• gBRCA1/2 • TNBC	NCT02595905
TBB	II	talazoparib	• HRD high • gHR/sHR mutation	NCT02401347
Ruby	II	rucaparib	• BRCAness • sBRCA1/2 mutation	NCT02505048
TOPACIO	II	niraparib + pembrolizumab	• TNBC • OvCa	NCT02657889

Select ongoing neoadjuvant/adjuvant trials of PARPi in breast cancer

Name	Phase	Arms	Clinicaltrials.gov
ISPY2	II	paclitaxel → AC irinotecan + talazoparib → AC	NCT01042379
MDACC	II	talazoparib x 6 mos	NCT02282345
NSABP B-55 (OlympiA)	III	olaparib vs placebo x 1 year	NCT02032823

Thank You!